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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, ALLISON M	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,689	SCHMIDT ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *5,6,8 and 20-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7 and 9-19* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/26/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-19, in the reply filed on 6/17/05 is acknowledged. The traversal is on the ground(s) that a search of subject matter of claims 1-19 would require a search of all art classifications 424 and 435, and thus would impose no serious burden on the examiner. This is not found persuasive because burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement and double patenting issues. Therefore searching the instant three patentably distinct inventions would, in fact, impose a serious burden on the examiner.

In response to the election of species requirement applicant elected, with traverse, the species of *bioactive agent* as the species of additional components to be adhered to the cell-free tissue replacement from claim 4, and *a drug* as the species of bioactive agent from claim 7. Due to the elections claims 5, 6 and 8 are withdrawn as being directed to non-elected species. With regards to applicant's traversal of the election of species requirements, as is proper in election of species practice, should a generic claim be found allowable the search will be extended to include additional species, see MPEP § 809.02.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application

Claims 1-4, 7, and 9-19 are being examined for patentability. Claims 1-40 are pending in the current application, of which 5, 6, 8, and 20-40 have been withdrawn from consideration.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because applicant's erroneously claimed priority under 35 USC 119(e) to the current US non-provisional application (10/672,689), instead of to the provisional application 60/414,278, filed 09/27/02.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Applicant's claim 2 is objected to because of a minor grammatical error: it appears the claim should read, "The method of claim 1, wherein the method for preparing the native, cell-free tissue replacement further comprises the step of..." or "The method of claim 1, further comprising the step of..."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, and 9-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant fails to provide sufficient written description of a representative number of sulfobetaine species which is required to claim the entire genuses of sulfobetaines. In the present specification applicant teaches sulfobetaine 10 (SB-10) and sulfobetaine 16 (SB-16) are suitable for use in the present method (See Spec Pg. 12 and 18); however, in view of the lack of relevant, identifying characteristics, such as structure or other physical or chemical properties, or functional characteristics, SB-10 and SB-16 fail to represent a representative number of sulfobetaine species required to claim the entire genus. In fact, the teaching of only the two species of SB-10 and SB-16 is still insufficient to claim even the genus of sulfobetaines which have hydrophilic tails of 10 to 16 carbons; as applicants have only shown success using sulfobetaines with exactly 10 and exactly 16 carbons, they have not provided evidence or support as to why any sulfobetaine with a hydrophilic tail within this range would be successful. Therefore, in view of the absence of disclosure of relevant, identifying characteristics of all suitable sulfobetaines, the teaching of SB-10 and SB-16 is not sufficient to show the applicant was in possession of the entire claimed genus of sulfobetaines, or even in possession of all sulfobetaines with a hydrophilic tail of 10 to 16 carbons. See *Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406. See MPEP § 2163.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7, and 9-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is directed to a method for preparing a native, cell-free tissue replacement comprising the steps of: a) soaking the tissue replacement for at least six hours in a solution comprising one or more sulfobetaines; b) washing the tissue replacement in one or more solutions of a buffered salt; c) extracting the tissue replacement in a mixture of one or more sulfobetaines with an anionic surface-active detergent; and d) washing the tissue replacement in one or more solutions of a buffered salt to remove the excess anionic surface-active detergent. The preamble claims a method for preparing a *native, cell-free* tissue replacement; however it is not clear from the body of the claim if the tissue replacement is obtained/harvested as a native, cell-free tissue replacement, or if the steps of the method are required to rid the tissue replacement of cells, so as to make it cell-free. Furthermore, it is not clear how the tissue replacement is *extracted* in step c) of the method. The term 'extracted' refers to withdrawing (as a juice or fraction) by physical or chemical process, or to treat with a solvent so as to remove a soluble substance (See Merriam-Webster Online Dictionary). It appears the tissue replacement is a solid mass that is transferred from the buffered salt solution to the solution of sulfobetaines and anionic surface-active detergent; therefore, the tissue replacement, per se, would not be *extracted*, but transferred or removed.

Applicant's claim 2 is directed to the method of claim 1, further comprising the step of "storing in a buffered salt solution until needed;" however, applicant fails to particularly point out what is stored in a buffered salt solution until needed. It appears applicant intended to claim a further step of "storing the tissue replacement in a buffered salt solution until needed;" examination was conducted as such.

Applicant's claim 4 is directed to the method of claim 1, further comprising the step of adhering one or more components to the tissue replacement before storing, wherein the component is a bioactive

agent. There is insufficient antecedent basis for the limitation "before storing" in this claim; claim 1 does not include a storage step, rather claim 3 includes a storage step, it appears that claim 4 should be dependent on claim 3.

Applicant's claim 9 is directed to the method of claim 1, wherein the tissue replacement is further modified into a select structure. It is unclear when this modification is to take place, and how. It is not clear if the tissue replacement is obtained/harvested in the desired structure, or if actions are taken to form the tissue replacement into the desired structure. If actions are taken to form the tissue replacement into the desired structure, it is not clear when this step occurs, after soaking in sulfobetaines, after the first washing in buffered salt, after extraction or after the final washing in a buffered salt.

Applicant's claim 11 is directed to the method of claim 1, wherein the anionic surface-active detergent comprises Triton X-200. The Sigma-Aldrich Detergent Product Index lists Triton X-200 as a non-ionic detergent, not an anionic surface-active detergent; therefore the claim is indefinite (See Sigma-Aldrich Detergent Product Index).

Applicant's claim 12 is directed to the method of claim 1, wherein the step of washing the tissue replacement comprises serial solutions of a buffered salt comprises three serial washes of 100 mM sodium and 50 mM phosphate for about 15 minutes each. First, there are two washing steps in claim 1, it is not clear which washing step claim 12 is referring to, if not both. Second, the language of the claim is so unclear as to render the claim indefinite. A suggestion to *grammatically* correct the claim is as follows: "The method of claim 1, wherein the step of washing the tissue replacement comprises three serial washes in a buffered salt solution comprised of 100 mM sodium and 50 mM phosphate, for about 15 minutes each wash." However, it remains unclear what concentrations comprise the solution series, as only a single salt solution is described; a serial wash would comprise washes of different salt concentrations.

Applicant's claim 14 is directed to the method of claim 13, wherein the tissue replacement is cleaned of fat and blood after harvesting and rinsed for several hours in deionized distilled water. The term "several hours" renders the claim indefinite, as no numerical reference is given in the claim so as to clearly define the method. Page 18 of the specification teaches soaking/rinsing a tissue replacement in deionized water for seven hours; if seven hours is required for the current method it must be clearly claimed.

Applicant's claim 17 is directed to the kit of claim 16, wherein the tissue replacement comprises a suture, tube, sheet, film, scaffold, valve, limb replacement, tissue transplant or a joint. It is not clear if the tissue replacement is to *further comprise* one of these elements, or if the tissue replacement is to be *shaped into* one of these structures, as in claim 9.

Applicant's claim 18 requires the tissue replacement of claim 17 to further comprise a cell, a polymer, a bioactive compound or combinations thereof. It is noted that if the tissue replacement further comprises a cell, it is no longer a cell-free tissue replacement. Thus inclusion of a cell would be repugnant to the preamble.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 15-17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Livesey et al (US Patent 5,336,616).

Applicant's claim 15 is directed to a native, cell-free tissue replacement made by the method of claim 1. Applicant's claim 16 is directed to a kit for tissue replacement comprising a sterile, cell-free tissue replacement of claim 15. Claim 17 requires the tissue replacement of claim 16 to comprise a suture, tube, sheet, film, scaffold, valve, limb replacement, tissue transplant or a joint. Claim 18 requires the tissue replacement of claim 17 to further comprise a cell, a polymer, a bioactive compound or a combination thereof. Claim 19 requires the tissue replacement of claim 17 to further comprise a sheet of instructions for use of the tissue replacement.

The native, cell-free tissue replacement product as claimed is determined to be a product-by-process claim. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Also note that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, such as instructions pertaining to the use of the product, the content of the printed matter will not distinguish it from the claimed product of the prior art. See *In re Gulack,* 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed Cir. 1983).

Livesey et al teach a native, cell-free tissue replacement created by detergent extraction of cells from harvested native tissue. The native, cell-free tissue replacement of Livesey et al forms a scaffold for a tissue transplant; Livesey et al teach examples wherein the cell-free tissue replacement forms a skin replacement (which applicant calls a film and sheet), a vascular conduit (which applicant calls a tube),

and a heart valve (See col. 23, ln 5-col. 30, ln 20) (Claims 15-17 and 19). Therefore the reference anticipates the claimed subject matter.

Claims 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Dennis et al (US Patent 6,207,451).

As stated above, the native, cell-free tissue replacement product as claimed is determined to be a product-by-process claim. See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Furthermore, note that the inclusion of printed matter that is not functionally related to the product, such as instructions as part of a kit, does not distinguish the claimed product from that of the prior art. See *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed Cir. 1983).

Dennis et al teach acellular muscle anchors for muscle tissue regeneration; the acellular anchors can be sterilized by ultraviolet light (which applicant calls sterile, native, cell-free tissue replacements) (Claims 15 and 16). The acellular muscle anchors consist of fragments of skeletal muscle that have been chemically acellularized. The acellular muscle anchors comprise ECM attachment molecules, including polymers laminin and collagen. The acellular anchors are seeded with myogenic precursor cells to form three-dimensional mammalian muscle constructs (See col. 3, ln 65-col. 4, ln 57 & col. 5, ln 59-65). Therefore the acellular muscle anchors of Dennis et al comprise polymers and cells, and because they come from acellularized skeletal muscle fragments, they also comprise transplanted tissue (which applicant calls tissue transplants) (Claims 17-19). Therefore, the references anticipate the claimed subject matter.

Claims 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Gulati et al (Brain Research, 1995).

As stated above, the native, cell-free tissue replacement product as claimed is determined to be a product-by-process claim. See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Furthermore, note that the inclusion of printed matter that is not functionally related to the product, such as instructions as part of a kit, does not distinguish the claimed product from that of the prior art. See *In re Gulack,* 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed Cir. 1983).

Gulati et al teach acellular basal lamina grafts derived from degenerated, decellularized sciatic nerve segments (which applicant calls native, cell-free tissue replacements). The acellular basal lamina grafts were produced by isolating degenerated sciatic nerve segments and subjecting the segments to a freeze/thaw process in liquid nitrogen, leaving only the basal laminae scaffold in the form of a tube. The acellular basal laminae grafts were then seeded with Schwann cells (See Pg. 120, col. 1). Therefore the acellular basal laminae grafts of Gulati et al comprise basal laminae tubes seeded with cells (Claims 17-19). Thus the reference anticipates the claimed subject matter.

Claims 15-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Tanagho et al (US Patent 6,371,992).

As stated above, the native, cell-free tissue replacement product as claimed is determined to be a product-by-process claim. See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Furthermore, note that the inclusion of printed matter that is not functionally related to the product, such as instructions as part of a kit, does not distinguish the claimed product from that of the prior art. See *In re Gulack,* 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed Cir. 1983).

Tanagho et al teach an acellular matrix graft isolated from muscle tissue for muscle tissue replacement and regeneration (which applicant calls native, cell-free tissue replacements) (Claims 15 and 16). The acellular matrix grafts consist of isolated muscle or nerve tissue that has been freed from cells and cellular components by mechanical, chemical and/or enzymatic methods to leave a scaffold

consisting essentially of collagen and elastin fibers (See col. 2, ln 16-30). The acellular matrix grafts can further comprise sutures that are used to stabilize the graft once implanted in the subject (See 6, ln 29-55). Therefore the acellular matrix graft of Tanagho et al comprises polymers collagen and elastin, surgical sutures, and because the grafts come from acellularized muscle or nerve tissue, they also comprise transplanted tissue (which applicant calls tissue transplants) (Claims 17-19). Therefore the reference anticipates the claimed subject matter.

Claims 15-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Atala (US Patent 6,376,244).

As stated above, the native, cell-free tissue replacement product as claimed is determined to be a product-by-process claim. See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Furthermore, note that the inclusion of printed matter that is not functionally related to the product, such as instructions as part of a kit, does not distinguish the claimed product from that of the prior art. See *In re Gulack,* 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed Cir. 1983).

Atala teaches a decellularized artificial organ created from an isolated organ or part of an organ that has undergone a series of detergent-based extractions that remove the cell membrane surrounding the organ and the cytoplasmic and nuclear components of the organ (which applicant calls a native, cell-free tissue replacement) (See col. 2, ln 43-63) (Claims 15 and 16). The decellularized artificial organs consists of an organ or part of an organ that has been decellularized to produce a three-dimensional scaffold; the scaffold can then be treated with bioactive agents and drugs, such as chondroitn-4-sulfate and dermatan sulfates and seeded with cells (See col. 4, ln 34-62 & col. 8, ln 55-68) (Claims 17-19). Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 9-14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livesey et al (US Patent 5,336,616), in view of "Detergent Properties and Applications" (Sigma-Aldrich).

Applicant's claim 1 is directed to a method for preparing a native, cell-free tissue replacement comprising the steps of: a) soaking the tissue replacement for at least six hours in a solution comprising one or more sulfobetaines; b) washing the tissue replacement in one or more solutions of a buffered salt; c) extracting the tissue replacement in a mixture of one or more sulfobetaines with an anionic surface-active detergent; and d) washing the tissue replacement in one or more solutions of a buffered salt to remove the excess anionic surface-active detergent.

Livesey et al teach a method for preparing a native, cell-free tissue replacement for transplantation. In an exemplified embodiment Livesey et al harvest external jugular veins and internal carotid arteries from animal donors, the veins are cleaned of surrounding tissue and fascia (which applicant calls cleaning of fat and blood) and are flushed with a buffered salt solution; the tissue is then soaked in a Decellularization Solution A (DSA) which comprises CHAPS, a zwitterionic detergent in a buffered salt base for one hour; the tissue is then given two ten minute washes in a buffered salt solution; the tissue is then soaked in a Decellularization Solution B (DSB) which comprises SDS (sodium dodecylsulfate), an anionic detergent, in a buffered salt base for one hour; the tissues are then given two final ten minute washings in a buffered salt base (See col. 26, ln 63-col. 27, ln 27 & col. 29, ln 15-40).

Though the example uses vascular conduits obtained from animals, Livesey et al also teach that the donor tissue can also be harvested from human cadavers (See col. 4, ln 56-68) (Claim 13).

Though Livesey et al use CHAPS as the zwitterionic detergent in the first decellularizing solution (DSA) in their example, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use any similar zwitterionic detergent, such as sulfobetaine SB-10 or SB-16 as the zwitterionic detergent in DSA (Claims 1, 3, and 10). One of ordinary skill in the art would have been motivated to use any zwitterionic detergent in place of CHAPS because zwitterionic detergents are functional equivalents, particularly with regards to their ability to solubilize membrane proteins (See Sigma Aldrich "Detergent"), and because Livesey et al teach that any similar zwitterionic detergent can be used in place of CHAPS. One would have had a reasonable expectation of successfully performing the method of Livesey et al using SB-10 or SB-16 because both sulfobetaines are functionally equivalent zwitterionic detergents that are capable of solubilizing membrane proteins to decellularize the tissue replacement.

Similarly, though Livesey et al use SDS as the anionic detergent in the second decellularizing solution (DSB) in their example, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use any similarly anionic or non-ionic detergent, such as Triton X-200 as the detergent in the DSB (Claim 11). One of ordinary skill in the art would have been motivated to use Triton X-200, a non-ionic detergent, in place of the anionic SDS because non-ionic detergents are gentler than anionic detergents and solubilize the proteins while maintaining the native subunit structure; thus the collagen ECM of the tissue replacement would be less affected by the non-ionic Triton X-200 than by the anionic SDS (See Sigma Aldrich "Detergent"). One would have had a reasonable expectation of successfully performing the method of Livesey et al using Triton X-200 in place of SDS in the DSB because both detergents are capable of solubilizing membrane proteins to decellularize the tissue replacement and because Livesey et al teach that any similar anionic or non-ionic detergent can be substituted in the DSB.

Though Livesey et al do not include the zwitterionic detergent along with the anionic detergent in the second decellularization solution (DSB), it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the zwitterionic detergent used in the first decellularization solution (DSA) (either CHAPS or SB-10 or SB-16) in the second decellularization solution, as well. All three types of detergents (zwitterionic, anionic, and non-ionic detergents), are known to solubilize proteins, which is why they are used by Livesey et al to extract cells from the collagen-containing tissue scaffold (See, e.g. Sigma-Aldrich "Detergent Properties and Applications"). One of ordinary skill in the art would have been motivated to include the zwitterionic detergent from the DSA (CHAPS, SB-10 or SB-16) in the DSB along with the anionic or non-ionic detergents (SDS or Triton X-200) in order to aid in the denaturation of proteins by increasing the amount of detergent the tissue replacement is exposed to. Therefore, including the zwitterionic detergent in the DSB would have been a routine matter of optimization to increase the degree of cell extraction in the tissue replacement which results from solubilized and denatured proteins. One would have expected success because all three of the detergents are known to solubilize and denature proteins, combining two different compositions that have the same effect to make a third composition with the same effect as the first two is prima facie obvious. Furthermore, one would not expect negative effects by including the zwitterionic detergent in the DSB because the anionic detergent used in the second decellularization solution (DSB) is much stronger then either the zwitterionic detergents or the non-ionic detergents, as anionic detergents completely disrupt cell membranes and denature proteins. Therefore, due to the gentler nature of the zwitterionic detergents in comparison to the anionic detergents, one of ordinary skill in the art would not be concerned with including zwitterionic detergents in the second decellularization solution (DSB).

Furthermore, though Livesey et al allow the tissue replacement to soak in the first decellularizing solution (DSA) and the second decellularizing solution (DSB) for only 30 minutes to 1 hour each, and not for "at least six hours" as presently claimed, the various lengths of the soaks are result effective variables,

they would be routinely optimized by one of ordinary skill in the art in practicing the method disclosed by Livesey et al. The effectiveness of the detergents is affected by the pH of the solution, temperature, and any agitation that is being applied to the tissue replacements. Similarly, though Livesey et al washes two times with PBS as the buffered saline wash, it would, again, have been obvious to one of ordinary skill in the art at the time the invention was made to perform serial washes using any suitable buffered saline solution to rinse the detergents from the tissue construct in between steps. The various buffered saline rinses as well as the number of washes and the length of each wash are all result effective variable that would routinely be optimized by one of ordinary skill in the art in practicing the invention of Livesey et al (Claim 12).

Livesey et al does teach that the harvested tissue is to be isolated and cleared of fascia (See col. 26, ln 63-col. 27, ln 27); however they do not teach rinsing the tissue for several hours in deionized distilled water prior to treatment. It would have been obvious to one of ordinary skill in the art at the time the invention was made to rinse the harvested tissue in deionized distilled water for a sufficient time in order to clean off excess tissue, fat and blood (Claim 14). One of ordinary skill in the art would have been motivated to rinse off the tissue prior to treatment in order to remove excess blood and tissue so that they do not interfere with the cell extraction. One would expect success cleaning off blood and tissue by rinsing with water for several hours because it is a routine, general procedure for cleaning any object.

Livesey et al teach that after decellularization the tissue replacement can be preserved by vitrification in a cryopreservative. Twenty-four hours prior to use the tissue replacement is rehydrated by submersion in buffered salt solution; thus the tissue is stored in buffered saline until use (See col. 27, ln 54-63) (Claim 2). However, though Livesey et al vitrify the tissue replacement for long term storage and then rehydrate the tissue replacement by hydration in buffered saline, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively store the tissue replacement directly in buffered saline. One of ordinary skill in the art would have been motivated to not vitrify the

tissue replacement, but rather store it directly in buffered saline until it is needed in cases when the tissue will be used within a few days and vitrification is unnecessary. One would expect success storing the tissue replacement directly in buffered saline because Livesey et al teach that the tissue replacement can be contained safely in buffered saline for extended periods, such as rehydration, with no adverse effects.

The native, cell-free tissue replacement of Livesey et al forms a scaffold for a tissue transplant; Livesey et al teach examples wherein the cell-free tissue replacement forms a skin replacement (which applicant calls a film and sheet), a vascular conduit (which applicant calls a tube), and a heart valve (See col. 23, ln 5-col. 30, ln 20). It would further have been obvious to one of ordinary skill in the art to form the cell-free tissue replacement of Livesey et al into a structure suitable for use in a tissue transplant, including the form of a suture, limb replacement, and/or joint (Claim 9). Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the cell-free tissue replacement of Livesey et al as part of a graft for any type of tissue replacement, including whole limb replacements as well as joint replacements (Claim 17). One of ordinary skill in the art would have been motivated to form the cell-free tissue replacement of Livesey et al into any desired shape for use as and/or with any type of tissue replacement because the cell-free tissue scaffold allows for invasion of autologous cells once implanted, which aids in the regeneration of natural, functional tissue. One would have expected success because Livesey et al have taught successful creation of skin, vascular and valve replacements that comprise the cell-free tissue replacements, therefore one would expect success using the tissue replacements in any type of tissue transplants.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4, 7 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livesey et al (US Patent 5,336,616), in view of Atala (US Patent 6,376,244).

Livesey et al teach a method for preparing a native, cell-free tissue replacement for transplantation and the native, cell-free tissue replacement formed. In an exemplified embodiment Livesey et al harvest external jugular veins and internal carotid arteries from animal donors, the veins are cleaned of surrounding tissue and fascia (which applicant calls cleaning of fat and blood) and are flushed with a buffered salt solution; the tissue is then soaked in a Decellularization Solution A (DSA) which comprises CHAPS, a zwitterionic detergent in a buffered salt base for one hour; the tissue is then given two ten minute washes in a buffered salt solution; the tissue is then soaked in a Decellularization Solution B (DSB) which comprises SDS (sodium dodecylsulfate), an anionic detergent, in a buffered salt base for one hour; the tissues are then given two final ten minute washings in a buffered salt base (See col. 26, ln 63-col. 27, ln 27 & col. 29, ln 15-40).

Though Livesey et al teach using CHAPS as the zwitterionic detergent in the first decellularizing solution and SDS as the anionic detergent in the second decellularizing solution, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use SB-10 or SB-16 as the zwitterionic detergent in the first decellularizing solution, and a combination of SB-10 or SB-16 and an anionic or non-ionic detergent in the second decellularizing solution. It would further have been obvious to the skilled artisan at the time the invention was made to optimize the times for the soaking and extractions in the first and second decellularizing solutions. See teachings above.

Livesey et al do not teach adding any bioactive agents or drugs to the decellularized tissue replacement after treatment with the detergents; however, Atala teaches it is beneficial to add drugs such as collagen, elastic fibers, glycoproteins, chondroitin-4-sulfate, chondroitin-6-sulfate, dermatan sulfate, keratin sulfate, etc, before seeding cells to decellularized tissue replacement scaffolds before seeding of cells in order to promote cellular adhesion and growth (See Atala, col. 8, ln 55-62). Therefore it would have been obvious to one of ordinary skill in the art to add bioactive agents and drugs, such as chondroitin-4-sulfate, to the decellularized tissue replacement scaffold of Livesey et al prior to use in

order to promote cell adhesion and cell growth (Claims 4, 7 and 18). One of ordinary skill in the art would have been motivated to add drugs to promote cell growth and adhesion in order to ensure cells infiltrate and adhere to the tissue replacement in order to create a functional tissue replacement. One would have expected success adding drugs and bioactive agents to the tissue replacement of Livesey et al because Atala et al teach successfully adding the drugs to a similar acellular tissue replacement (See Atala, col. 8, ln 55-62). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER